Historical Perspectives

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The difficulty with a broad title such as this is where to start. One might have begun with quotations from Hippocrates but there is no time for that. We can move quickly to the last century and here we cannot pass over the pronouncements of Virchow in 1865[1] on the mucous plug at the mouth of the common bile duct as the cause of catarrhal jaundice, for his description was a stumbling block to an understanding of the basic pathology of the disease up to nearly 1940. In fact an annotation in the *Lancet* of March 1940 commences with "It is now accepted that there are two forms of mild jaundice in this country, one due to catarrh of the common bile duct associated with duodenitis, the other to hepatitis", and a further annotation on hepatitis in the *British Medical Journal* of August, 1940 included the statement "There is still uncertainty about not only its etiology but also its pathology". Many famous physicians, including Sir Arthur Hurst in the United Kingdom, were firm believers in the theory of the mucous plug although it is highly unlikely that any of them had ever seen more than one or two such cases at necropsy.

The most pertinent incident for a starting point is the outbreak of hepatitis in shipyard workers in Bremen described by Lurman in 1885.[2] The disease occurred several months after their vaccination against smallpox with lymph obtained from the vesicles of other vaccinated humans. Lurman's very clear description of the events leaves little doubt that this was an example of long-incubation-period hepatitis almost certainly caused by blood contamination of the lymph, as inoculation was performed in the staff of three different buildings on the same day with the same material, and cases occurred in all groups.

It is possibly strange that no record of other such events before the 20th century has been found in view of the practice of using human lymph for smallpox vaccination and the widespread practice of tattooing, particularly among service personnel, and sailors in general. Presumably the occurrence of leptospirosis, malaria, yellow fever and other such diseases obscured the picture. Yet the rapidity with which arsphenamine jaundice was seen in different countries in 1914-18 after the introduction of venepuncture, the Wassermann test for syphilis and the new chemotherapy of Ehrlich suggests that one or more hepatitis viruses were in circulation awaiting to be disseminated. Another landmark one must mention was the discovery of Leptospira reported by Inada and his colleagues in 1916. As is so often the case with a new discovery, it was thought that it was going to supply the key to the etiology of most epidemics of jaundice and many cases of catarrhal jaundice were wrongly ascribed to it, but soon failure to recover Leptospira from patients in outbreaks helped to establish catarrhal jaundice as a separate entity. A leukopenia with a relative increase of lymphocytes and large mononuclear cells in catarrhal jaundice was recognized as a point in the differential diagnosis from leptospirosis at this time.

The possibility of unintentional transmission of hepatitis by blood was recognized in Sweden in 1925[3] among diabetics attending a laboratory for blood tests. This was shortly after the isolation of insulin by Banting and Best in Toronto and the Swedish patients had not received insulin. One can imagine the consternation that might have been caused if their hepatitis had occurred after injection of the new wonder drug and the present world-wide rapid dissemination of information in the lay and medical press had prevailed at that time.

One must not pass over the observations of our Swedish colleagues without drawing attention to the nu-

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merous valuable contributions to our knowledge of various aspects of hepatitis which they have made by their epidemiological studies and it was unfortunate that their reports were not read more widely before 1939.

In 1930, H. C. Brown at the Wellcome Research Institute, London developed hepatitis forty days after receipt from Pickles in Yorkshire of blood from patients with catarrhal jaundice which Brown tested for leptospiral antibodies.

After several years during which reports of clinical, biochemical, pathological and epidemiological investigations of outbreaks of hepatitis in much of the temperate zone were published, attention was suddenly focused on the potential icterogenicity of serum from some normal persons in England as a result of two unrelated incidents.[4-6]

In 1934 a laboratory assistant of Findlay developed hepatitis three and one-half months after his inoculation with neurotropic yellow fever virus and human yellow fever immune serum, but the recognition of a number of cases of "yellow fever vaccine jaundice" did not occur until 1936-37, when as a result of the introduction of the new tissue culture vaccine in 1936 more than 1000 persons were inoculated, before going to West Africa.[4] The interval between inoculation and hepatitis was two to six months. We concluded that there was some toxic or infective agent present in the serum from normal adults which we had used in the tissue culture medium.

At about the same time as the above the medical department of London County Council had collected large pools of adult plasma for measles prophylaxis. About 36,000 children received 366 litres from 3000 donors over a period of 10 years with no ill effect, so that it was a great shock when a number of cases of hepatitis with some deaths occurred in children in Oxford 60 to 90 days after inoculation from a single batch of this serum.[5] There were additional cases[6] among children inoculated from the same batch in an institution about 120 miles away. The relationship of this blood-transmitted disease to infective hepatitis was left in doubt, particularly as two uninoculated children in the institution developed jaundice about two months later.

In the U.S.A. the stimulus to conduct research in this problem came from the unfortunate production there in 1939 of a number of batches of yellow fever vaccine containing the serum hepatitis virus. The urge to study infective hepatitis more intensively in the British forces arose at an early date in the Middle East. As in World War I, epidemiological studies in the Mediterranean area eventually pointed to the importance of the fecal/oral route of transmission as opposed to the hypothesis of oropharyngeal transmission favoured in temperate and other climates previous to 1940. Prof. Van Rooyen's desire to investigate the problem in British military volunteers in 1942 in the Middle East was not supported, but specimens which he and his colleagues had collected were sent to one of the U.S. army teams of investigators in New Haven.

Meanwhile in England further cases of serum hepatitis had been caused by a pool of mumps convalescent plasma used in a large military unit[7] and yellow fever vaccine-induced cases were occurring in recently arrived American service personnel.[8] As I was the only worker in this particular field in the U.K., Findlay having gone off soon after the beginning of the war to what he considered more interesting work in West Africa, specimens flooded in from all sides including the above and also from patients with apparent naturally occurring infective hepatitis. I do not remember at this point what prompted me to turn to studies in volunteers other than several years of continually negative results in the laboratory, nor do I know how the decision was taken in the U.S.A., except that there was an official army board which presumably decided on the matter. I was working almost in a vacuum except for the occasional visits from service officers, but moral support came particularly from Prof. (then Brigadier) John Gordon of the Harvard School of Public Health and Drs. MacNair Scott and Alex Steigman who had come to England with the Harvard Red Cross Hospital. The main job for which I was reserved in London was the production of yellow fever vaccine and it was a sergeant of one of the medical officers at a unit near London, whom I met as a result of supplying this material, who was the first volunteer. Chick embryo tissue cultures had been inoculated with serum from the patients with jaundice due to mumps plasma and yellow fever vaccine and several sub-cultures had been carried out by the time we finally organized some tests. I had also obtained the co-operation of two U.S. army yellow fever vaccine hepatitis convalescents as possible controls to the sergeant. As erythematous and morbilliform rashes had been prominent in those who received the icterogenic mumps plasma it seemed worth while to inoculate the material intradermally to see if a skin test reaction might be obtained which would be helpful in diagnosis. A few weeks later I obtained the co-operation of another normal person, two who had what was diagnosed as infective hepatitis six months previously, six who were convalescent from the American yellow fever vaccine hepatitis and two convalescent from mumps plasma hepatitis. Fluid from uninoculated tissue cultures and cultures of the yellow fever 17D virus without serum were used as control inoculations in the intradermal tests. There was no specific skin reaction in the convalescent serum hepatitis patients but in two successful takes in the other volunteers. In the sergeant mentioned above and in one of the convalescent infective hepatitis patients, skin reactions in the form of weals in one and an erythematous rash in the other occurred at the onset of their illness.[9] I refer to these specific points here because of the renewed attention that has been given recently to the possible role of antigen/antibody reactions in the production of Australia antigen-associated hepatitis. My colleague, Dr. John Bauer, also pursued this problem by attempting to develop an *in vitro* test with sensitized animal gut in the traditional physiological laboratory type test but with no success. Dr. James Gear and others at the Rockefeller Institute also investigated this question in 1942 and obtained positive precipitin reactions between acute and convalescent sera of patients with serum hepatitis. However, this also occurred when the livers of some fatal cases and some animal tissues were used as antigens which suggested that this was probably a non-specific reaction.

Much of what we did was done in parallel at the same time by the two groups of investigators, which included Drs. Paul, Stokes, Havens, Neefe and others, in the U.S.A. In addition they were able to test the value of the gammaglobulin fraction of blood newly prepared by Cohn and his colleagues as a prophylactic against infective hepatitis[10] and its ineffectiveness against serum hepatitis.

The next significant finding was the infectivity of suspensions of stools from infectious hepatitis patients given orally in England, and in the U.S.A. both orally and by subcutaneous inoculation of Seitz filtrates of these suspensions.[11,12] Instead of removing bacteria by a Seitz filter I had treated suspensions with 10% ether in the cold, a method which Dr. Francis had recently reported in connection with the preparation of fecal specimens for injection into monkeys for the isolation of poliovirus. In spite of all epidemiological investigations and one or two questionable transmissions by Voegt in Germany in 1942 and by us in the United Kingdom, attempts at incrimination of the nasopharynx or the oropharynx as a source of virus were a failure.

One day in 1942, I received a message to go to Whitehall to see one of the senior medical advisers and when I arrived I was asked "what is this yellow fever vaccine and how dangerous is it?" After explaining its constitution and the possibility of a mild reaction four to five days after inoculation I was told that the Cabinet was at that moment debating whether or not Mr. Churchill should be allowed to go to Moscow, which he wished to do in a few days' time. The yellow fever vaccine inoculation was theoretically essential before he could fly through the Middle East, but I explained that no antibody would be produced before seven to ten days so that there would be little point in giving the vaccine. It was finally decided that the vaccine would not be used, and the administrators would take care of the situation. Several months later I received an irate call from the Director of Medical Services of the R.A.F., who had been inoculated from the same batch of vaccine which would have been used for Mr. Churchill, and was informed that the D.G. had spent a very mouldy Christmas with hepatitis about 66 days after his inoculation. This was the first I knew that we were in for trouble again with our vaccine after a lapse of five years. Unfortunately, owing to the war, I had never received the information that it had been found in Brazil that serum was not necessary for stabilization of the 17D virus in the vaccine. I will leave you to speculate on what might possibly have been the effect on the liver of our famous statesman and our ultimate fate if he had received the icterogenic vaccine.

As I mentioned earlier, the introduction of venepuncture and arsenotherapy resulted in the first known widespread activation of blood borne hepatitis, and although the idea of an infective element had occurred to Ruge in Germany and J. H. Stokes in the U.S.A. after World War I, it was not until about 1942 that some bacteriologists and pathologists who had been seconded to the army began to see the possibility of syringe transmission occurring in V.D. treatment centres; the idea probably germinated in the minds of several of us at the same time when we had given thought to the minute amounts of blood that appeared to be capable of producing the disease.[13] However, the idea of arsenical intoxication was quite firmly fixed in the minds of most venereologists and I can well remember the atmosphere at a meeting of the Society for the Study of Venereal Disease in London in March 1943 when, after a main paper on arsenotherapy jaundice and expression of views by a number of discussants, I rose to suggest that a hepatitis virus in blood might be transmitted by imperfectly sterilized syringes and needles in their clinics.[14] My only vocal support was from Prof. John McMichael. It was not until Salaman and others had shown that the incidence could be controlled by proper attention to sterilization of equipment and we had successfully transmitted hepatitis to volunteers through the injection of blood of two patients from a special treatment clinic[15] that many venereologists were convinced of this point, at least in the U.K.

Eventually the concept of healthy carriers of virus B[16] and their danger as blood donors was established[17,18] and this was when the immunological status of infective and serum hepatitis[15,19] revealed a possible variation of patterns.

Earlier I referred to confusion caused by 19th century pathologists. Although a few isolated reports between 1918 and 1939 suggested that inflammation of the liver rather than duodenitis was the predominant lesion, it was not until Roholm and Iversen[20] described the changes they found in specimens obtained by needle biopsy of the liver from patients during life that the true nature of the parenchymal lesions was established.

Our own work in volunteers stopped immediately on cessation of war in 1945,[21] but work on serum hepatitis was continued by the staff of the National Institutes of Health in Washington and others.

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Discussion

DR. MOSLEY: Would you like to comment on the search for person-to-person transmission of hepatitis following yellow fever vaccination or similar other circumstances in World War II?

DR. MACCALLUM: Serum hepatitis or virus B Australia antigen-associated agents are transmitted by other routes than the introduction of blood, but this is a very uncommon event.

QUESTION: Dr. Gocke has produced arthritis with hepatitis. Dr. MacCallum has cured it. I wonder if Dr. Gocke might want to comment on the apparent paradox.

DR. GOCKE: I think it is probably proper to say that we have observed a polyarteritis-type syndrome which has been associated in some cases with joint involvement. I really don't think there is necessarily a paradox here. Indeed, probably different mechanisms are involved. I, too, am fascinated by the old observations of the apparent benefit to rheumatoids from concomitant hepatitis. I think that these two phenomena must involve different mechanisms.

DR. CHALMERS: We are all bothered now by the fact that up to 50% of patients with apparently non-epidemic hepatitis coming into the hospital are positive for Australia antigen in spite of the usual lack of history of parenteral injections. It seems to me that Findlay and Martin were the first and maybe the only people to demonstrate that yellow fever vaccine hepatitis could be spread by nasopharyngeal washings, and I wonder if it could be that this is what is happening in the present instance in which Type B virus seems to be spread by non-parenteral inoculation. In other words is it another kissing disease?

DR. MACCALLUM: The experiments to which you refer were carried out in West Africa in volunteers, and I was never very happy about this report. The incubation periods in the three cases which Findlay and Martin described were strange in that they were only 20 to 30 days in two out of the three cases and 50 days in the third. Whether this was some kind of a sensitization phenomenon or what the mechanism was is difficult to understand. We failed to induce hepatitis in volunteers in England by the intranasal inoculation of aliquots of the icterogenic serum which was used in the yellow fever vaccine which caused the hepatitis cases from which Findlay and Martin collected the nasopharyngeal washings for their experiments. We had one experience in England of apparent transmission with nasopharyngeal washings in volunteers who were inoculated with throat washings and swabbings from patients with "arsphenamine" serum hepatitis (MacCallum *et al.* 1951) (MacCallum 1972, in the press). These materials were inoculated on several occasions into these different individuals and two of the 17 developed hepatitis 100 and 104 days after their first inoculation; these two individuals had both received material from the same pools on two different days, as had a large proportion of the other 15 volunteers. I came to believe afterwards that it is possible that, if you rub throat swabs hard enough on the backs of people's throats and tonsils, and if you wash large amounts of saline through the nose and nasopharynx, the chances are quite good that you will pick up a certain amount of blood. It seems to me that in the transmission experiments, what we might have been doing was transmitting small amounts of blood in these washings. We have had only one case of Australia antigen-associated hepatitis in two years among all the cases of hepatitis in hospital in Oxford, and this was in an infant who almost certainly contracted the disease during birth from her mother who was a carrier. I think you must mention the community where you are speaking from when discussing whether or not there is a high rate of a "natural" method of transmission, and under what conditions this occurs.

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